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(54) Title: METHODS FOR PREVENTION OF ACCUMULATION OF AMYLOID BETA PEPTIDE IN THE CENTRAL NERVOUS SYSTEM

(57) Abstract: A method of either inhibiting the formation of Aβ or stimulating the formation of sAPP comprises administering to a patient with a neurological disease or a patient at risk of developing a neurological disease an effective quantity of a purine derivative or analogue, a tetrahydroindolone derivative or analogue, or a pyrimidine derivative or analogue. If the compound is a purine derivative, the purine moiety can be guanine or hypoxanthine. The neurological disease can be a neurodegenerative disease such as Alzheimer's disease or a neurodevelopmental disorder such as Down's syndrome. Typically, the compound can pass through the blood-brain barrier. The purine moiety can be hypoxanthine or guanine. A particularly preferred purine derivative is N-4- carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide.

METHODS FOR PREVENTION OF ACCUMULATION OF AMYLOID BETA PEPTIDE IN THE CENTRAL NERVOUS SYSTEM

CROSS-REFERENCES

This application claims priority from Provisional Application Serial No. 60/216,845, filed July 7, 2000, by Michelle S. Glasky, Debomoy K. Lahiri, and Martin R. Farlow, and entitled "Methods for Prevention of Accumulation of Amyloid Beta Peptide in The Central Nervous System by Treatment with Bifunctional Purine Analogues," which is incorporated herein in its entirety by this reference.

BACKGROUND OF THE INVENTION

This invention is directed to methods for blockage of accumulation of amyloid beta-peptide (Aβ) in patients with neurological diseases including neurodegenerative diseases such as Alzheimer's disease and neurodevelopmental disorders such as Down's syndrome, particularly with purine derivatives or analogues, pyrimidine derivatives or analogues, or tetrahydroindolone derivatives or analogues.

Alzheimer's disease (AD) is characterized by the cerebrovascular deposition of amyloid beta-peptide (Aβ) which is derived from a large integral membrane glycoprotein, β-amyloid precursor protein (APP). APP is processed by three proteases designated as α-, β-, and γ-secretases. The α-secretase cleaves APP within Aβ (between residues 16 and 17) to the secreted derivative sAPP and precludes Aβ formation. The processing of APP by α-secretase is altered by growth factors and M1 and M3 cell surface receptors. These agents increase sAPP secretion and also reduce Aβ production in some cell types. The stimulation of sAPP secretion by growth factors is partly mediated by protein kinase C (PKC) and partly by tyrosine kinase activities. The growth factors that increase sAPP secretion include nerve growth factor (NGF) and basic fibroblast growth factor (bFGF). Purine derivatives, such as AIT-082, have been shown to stimulate secretion of neurotrophic growth factors.

Therefore, there exists a need for methods that can inhibit the formation of Aβ and can stimulate the formation of sAPP in patients with neurological diseases, including neurodegenerative diseases such as AD and neurodevelopmental disorders such as Down's syndrome. Preferably, these methods should be able to be combined with methods that enable active compounds to bypass the blood-brain barrier, making

combined therapy more efficient. These methods should also be suitable for use with compounds or pharmaceutical compositions that can stimulate nerve growth or regeneration in patients neurological diseases, including neurodegenerative diseases such as AD and neurodevelopmental disorders such as Down's syndrome, thus reversing the course of the disease.

SUMMARY

One embodiment of the present invention is a method of either inhibiting the formation of Aβ or stimulating the formation of sAPP by administering to a patient with a neurological disease or a patient at risk of developing a neurological disease an effective quantity of a compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L though a carbonyl group wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

The purine moiety can be selected from the group consisting of hypoxanthine and guanine, as well as other purine moieties. A number of purine derivatives suitable for use in methods according to the present invention are disclosed. A particularly preferred purine derivative is N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide. Preferably, the compound is capable of passing through the blood-brain barrier.

The neurological disease can be a neurodegenerative disease, such as, but not limited to, Alzheimer's disease (AD). Alternatively, the neurological disease can be a neurodevelopmental disorder such as, but not limited to, Down's syndrome.

BRIEF DESCRIPTION OF THE DRAWINGS

The following invention will become better understood with reference to the specification, appended claims, and accompanying drawings, where:

Figure 1 is a photograph of the transferred proteins of a gel electrophoresis (immunoblot) of proteins from PC12 cells in culture treated with NGF, bFGF, or the bifunctional purine derivative N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide (also known as AIT-082) probed with anti-APP antibody with immunodetection by an enzymatic color method; and

Figure 2 is a graphical representation of the intensity of the bands of a Western immunoblot, similar to Figure 1, as determined by densitometry scanning.

DESCRIPTION

We have discovered that the bifunctional purine derivative N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide (also known as AIT-082 and leteprinim potassium), which bypasses the blood-brain barrier and is transported into brain by a nonsaturable mechanism, can act to increase the secretion of sAPP and therefore to decrease the formation of Aβ. This property of increasing the secretion of sAPP and decreasing the formation of Aβ, therefore, should also be possessed by other bifunctional purine analogues, as discussed below, as well as other compounds, including tetrahydrolone derivatives and analogues, and pyrimidine derivatives and analogues.

Therefore, in general, a method according to the present invention is a method of either inhibiting the formation of Aβ or stimulating the formation of sAPP comprising administering to a patient with a neurological disease or a patient at risk of developing a neurological disease an effective amount of a compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the

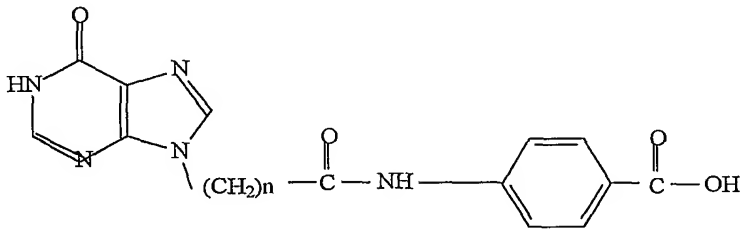
group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L through a carbonyl group wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

Typically, a compound useful in a method of the present invention is capable of passing through the blood-brain barrier.

In one preferred embodiment of methods according to the present invention, the moiety A is a purine moiety.

In one alternative, A is a substituted or unsubstituted hypoxanthine moiety. Typically, in this alternative, L has the structure $–(CH_2)_n$- where n is an integer from 1 to 6.

The compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP can be a compound of formula (I)

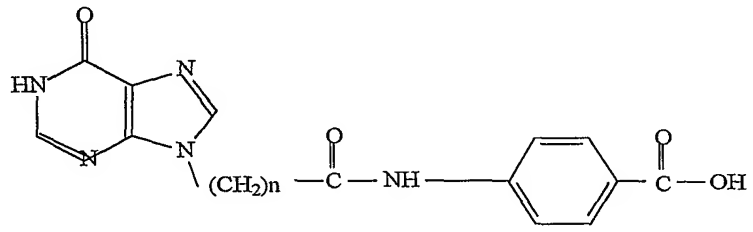


(I)

where n is an integer from 1 to 6 and R is hydrogen or lower alkyl or is a salt or prodrug ester of a compound of formula (I) wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl. Typically, the compound is a compound of formula (I) wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl. Typically, R is hydrogen, and the compound is N-4-[[3-(6-oxo-1,6-dihydropurin-9-yl)-1-oxopropyl]

amino] benzoic acid, designated AIT-082. Alternatively, R is ethyl, and the compound is N-4-[[3-(6-oxo-1,6-dihydropurin-9-yl)-1-oxopropyl] amino] benzoic acid ethyl ester.

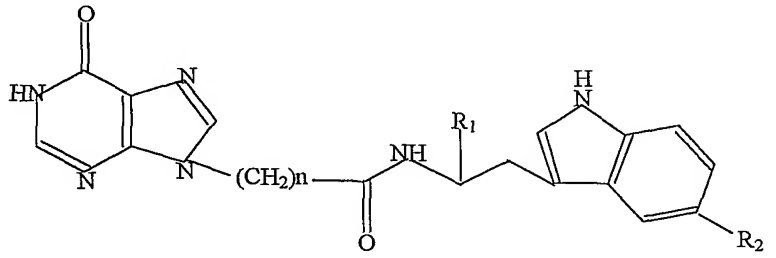
When the purine moiety is hypoxanthine, a preferred purine derivative is a compound of formula (I)



(I)

wherein n is an integer from 1 to 6 or of a salt or prodrug ester of formula (I) wherein n is an integer from 1 to 6. Typically, the purine derivative is a compound of formula (I) wherein n is an integer from 1 to 6. Preferably, n is 2 and the compound is N-4-carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide, also known as AIT-082. The activity of this compound is described further in the Example.

Alternatively, the purine derivative can be a 9-substituted hypoxanthine derivative of formula (II)



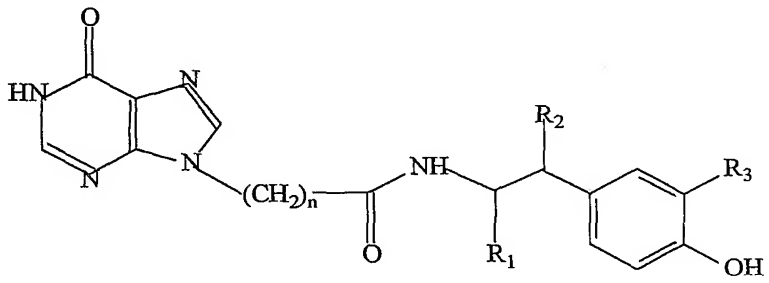
(II)

wherein n is a integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, where W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, and R_2 is selected from the group consisting of H and OH.

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H and R_2 is OH and the purine derivative is N-(2-(5-hydroxyindol-3-yl))ethyl-3-(6-oxohydropurine-9-yl) propanamide. In this alternative, for another particularly

preferred purine derivative, n is 2, R_1 is H and R_2 is H and the purine derivative is N-(2-indol-3-yl)ethyl-3-(6-oxohydropurin-9-yl) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, and R_2 is OH and the purine derivative is N-(1-carboxyl-(2-(5-hydroxyindol-3-yl))ethyl-3-(6-oxohydropurin-9-yl) propanamide.

As another alternative, the purine derivative can be a 9-substituted hypoxanthine derivative of formula (III)

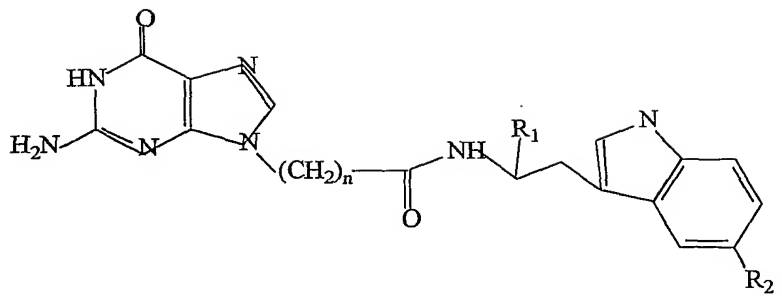


(III)

wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting of H and OH.

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H, R_2 is H, and R_3 is OH, and the purine derivative is N-(2-(3,4-dihydroxyphenyl))ethyl-3-(6-oxohydropurin-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H, R_2 is OH, and R_3 is OH, and the purine derivative is N-(2-hydroxy-2-(3,4-dihydroxyphenyl))ethyl-3-(6-oxohydropurin-9-yl) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, R_2 is H, and R_3 is OH, and the purine derivative is N-(1-carboxyl-2-(3,4-dihydroxyphenyl))ethyl-3-(6-oxohydropurin-9-yl) propanamide.

When the purine moiety is guanine, one preferred purine derivative is a 9-substituted guanine derivative of formula (IV)

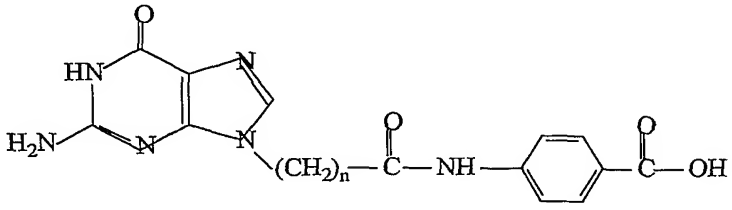


(IV)

wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, or W_1 is lower alkyl, amino, or lower alkylamino, and R_2 is selected from the group consisting of H and OH.

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H, and R_2 is OH, and the purine derivative is N-(2-(5-hydroxindol-3-yl))ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide. In this alternative, for another particularly preferred purine derivative, n is 2, R_1 is H, and R_2 is H and the purine derivative is N-(2-(2-indol-3-yl)ethyl))-3-(2-amino-6-oxohydropurin-9-yl)) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, and R_2 is OH, and the purine derivative is N-(1-carboxyl)-(2-(5-hydroxyindol-3-yl))ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

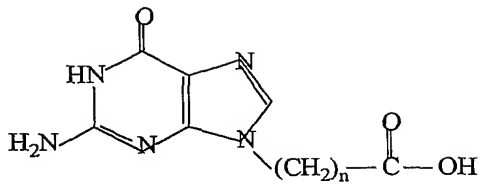
Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (V) wherein n is an integer from 1 to 6.



(V)

In this alternative, for one particularly preferred purine derivative, n is 2 and the compound is N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

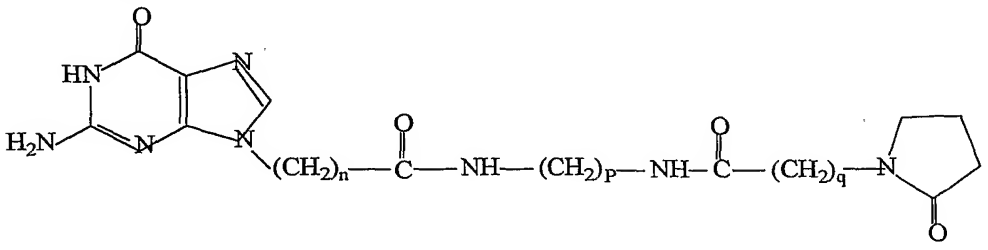
Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (VI) wherein n is an integer from 1 to 6.



(VI)

In this alternative, for one particularly preferred purine derivative, n is 2 and the compound is 3-(2-amino-6-oxohydropurine-9-yl) propanoic acid.

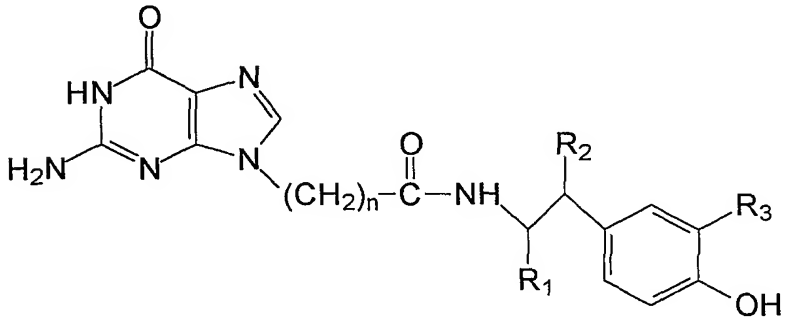
Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (VII) wherein n is an in integer from 1 to 6, p is an integer from 1 to 6, and q is an integer from 1 to 3.



(VII)

In this alternative, for one particularly preferred purine derivative, n is 2, p is 2, and q is 1, and the purine derivative is N-[2-[[2-(2-oxopyrrolidin-1-yl)-1-oxoethyl]amino]ethyl] propanamide.

Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (VIII) wherein R_1 is selected from the group consisting of H, COOH, and $COOW_1$, where W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting of H and OH.

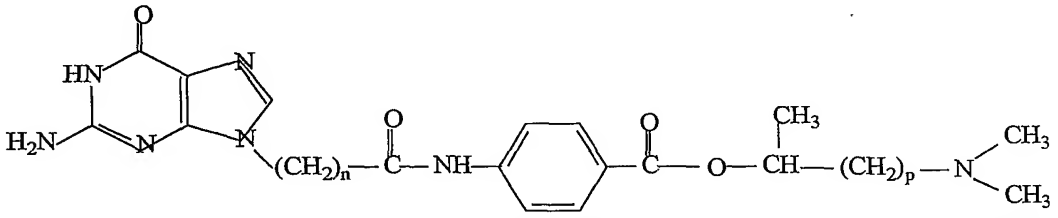


(VIII)

In this alternative, for one particularly preferred purine derivative, n is 2, R_1 is H, R_2 is H, and R_3 is OH, and the purine derivative is N-(2-(3,4-dihydroxyphenyl)ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide. In this alternative, for another

particularly preferred purine derivative, n is 2, R_1 is H, R_2 is OH, and R_3 is OH, and the purine derivative is N-(2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide. In this alternative, for still another particularly preferred purine derivative, n is 2, R_1 is COOH, R_2 is H, and R_3 is H and the compound is N-(1-carboxyl-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

Alternatively, the purine derivative can be a 9-substituted guanine derivative of formula (IX) wherein n is an integer from 1 to 6 and p is an integer from 1 to 3.

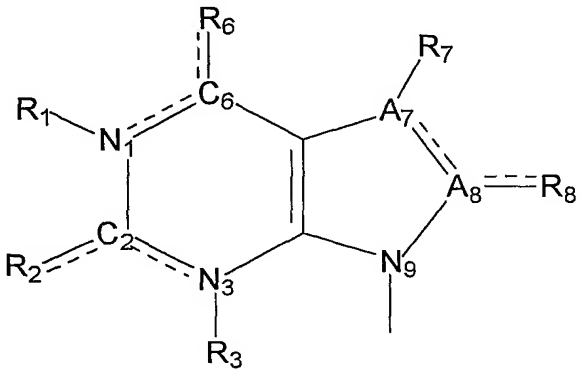


(IX)

In this alternative, for one particularly preferred purine derivative, n is 2, p is 1, and the compound is the 1-(dimethylamino)-2-propyl ester of N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

Other bifunctional hypoxanthine derivatives suitable for use in methods according to the present invention are disclosed in U.S. Patent No. 5,091,432 to Glasky, incorporated herein by this reference. Other bifunctional guanine derivatives suitable for use in methods according to the present invention are disclosed in U.S. Patent Application No. 09/419,153, by Glasky et al., incorporated herein by this reference.

More generally, purine-based compounds suitable for use in methods according to the present invention are compounds in which A is a substituted or unsubstituted 9-atom bicyclic moiety in which the 5-membered ring has 1 to 3 nitrogen atoms, the bicyclic moiety having the structure of formula (X)



(X)

where:

(1) if the bond between N_1 and the bond between C_5 is a single bond,

then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(2) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(3) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(4) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can

be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(5) A_7 and A_8 are C or N;

(a) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a single bond, then the bond between A_8 and R_8 is two single bonds to two hydrogen atoms or is a double bond in which R_8 is O or S and R_7 is two hydrogen atoms;

(b) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a double bond, then R_7 is hydrogen, the bond between A_8 and R_8 is a single bond and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(c) if A_7 and A_8 are both N, then the bond between A_7 and A_8 is a double bond, and R_7 and R_8 are not present;

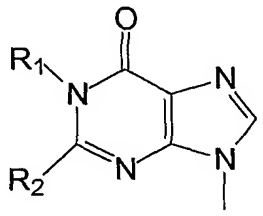
(d) if A_7 is C and A_8 is N, then the bond between A_7 and A_8 is a double bond, R_7 is hydrogen, and R_8 is not present;

(e) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a double bond, then R_7 is not present, the bond between A_8 is a single bond, and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(f) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a single bond, then R_7 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, the bond between A_8 and R_8 is a double bond, and R_8 is O or S; and

(6) N_9 is bonded to L; with the proviso that A does not have the structure of an unsubstituted guanine or hypoxanthine.

The purine moiety can be a purine moiety of formula (XI)



(XI)

in which:

(1) R_1 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, and heteroaralkyl; and

(2) R_2 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl,

aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylokoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroarylkylaminocarbonyl in which the alkyl portions could be cyclic and can contain from one to three heteroatoms which could be N, O, or S, with the proviso that both R_1 and R_2 are not hydrogen and that R_1 is not hydrogen when R_2 is amino.

The purine moiety of formula (XI) is a hypoxanthine or a guanine derivative but excludes unsubstituted hypoxanthine, in which R_1 and R_2 are hydrogen, and unsubstituted guanine, in which R_1 is hydrogen and R_2 is amino.

In one particularly preferred embodiment, R_1 is butyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is benzyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is dimethylaminoethyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is cyclopentyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is cyclohexylmethyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is cyclopropylmethyl and R_2 is hydrogen.

In another preferred embodiment, R_1 is hydrogen and R_2 is phenyl.

In another preferred embodiment, R_1 is hydrogen and R_2 is trifluoromethyl.

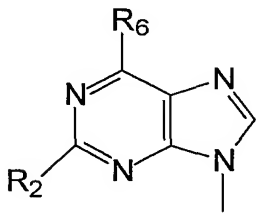
In another preferred embodiment, R_1 is hydrogen and R_2 is butyl.

In another preferred embodiment, R_1 is butyl and R_2 is butyl.

In another preferred embodiment, R_1 is hydrogen and R_2 is methyl.

In another preferred embodiment, R_1 is hydrogen and R_2 is phenylamino.

Alternatively, the purine moiety can be a purine moiety of Formula (XII)



(XII)

in which:

(1) R_2 is selected from the group consisting of hydrogen, halo, amino, OQ_3, SQ_3, $NHNH_2$, $NHOQ_3$, NQ_3Q_4, or NHQ_3, where Q_3 and Q_4 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_3 and Q_4 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3 where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

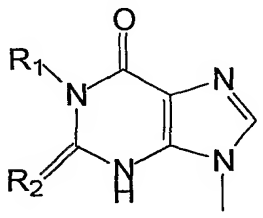
(2) R_6 is selected from the group consisting of hydrogen, halo, amino, OQ_5, SQ_5, $NHNH_2$, $NHOQ_5$, NQ_5Q_6, or NHQ_6, where Q_5 and Q_6 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_5 and Q_6 are present together and are alkyl, they can be taken together to form a 5- or 6- membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

In one preferred example of this embodiment, R_2 is hydrogen and R_6 is $-NH_2$ or $-N(CH_3)_2$.

In another preferred example of this embodiment, R_2 is hydrogen and R_6 is Cl.

In yet another preferred example of this embodiment, R_2 is $-NH_2$ and R_6 is Cl.

In another alternative, the purine moiety is the purine moiety of Formula (XIII)



(XIII)

in which:

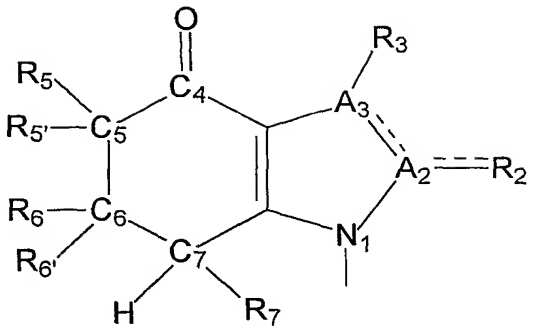
(1) R_1 *is* hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl; and

(2) R_2 *is* O or S.

Preferably, in this embodiment, R_1 is hydrogen and R_2 is O or S.

Particularly preferred purine-based compounds for use in methods according to the present invention include: (1) 4-[3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (2) 4-[3-(1-butyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (3) 4-[3-(1-methyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (4) 4-[3-(1-(2-dimethylaminoethyl)-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (5) 4-[3-(2,6-dioxo-1,2,3,6-tetrahydropurin-9-yl)propionylamino] benzoic acid ethyl ester; (6) 4-[3-(6-methoxypurin-9-yl)propionylamino] benzoic acid ethyl ester; (7) 4-[3-(6-dimethylaminopurin-9-yl)propionylamino] benzoic acid ethyl ester; (8) 4-[3-(2-amino-6-chloropurin-9-yl)propionylamino] benzoic acid ethyl ester; (9) 4-[2-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl)propionylamino]benzoic acid ethyl ester; (10) 4-[2-(2-butyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino]benzoic acid ethyl ester; (11) 4-[2-(6-oxo-2-phenyl-1,6-dihydropurin-9-yl)propionylamino]benzoic acid ethyl ester; (12) 4-{[3-(6-chloropurin-9-yl)propionyl]methylamino} benzoic acid methyl ester; (13) 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-[3-(2-oxopyrrolidin-1-yl)propyl] propionamide; (14) 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-{2-[2-(2-oxopyrrolidin-1-yl)acetylamino]ethyl} propionamide; (15) N-3-(2-oxopyrrolidin-1-yl)propyl]-3-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl) propionamide; and (16) 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-(3-morpholin-4-yl-propyl) propionamide.

In another alternative of methods according to the present invention, the compound is a tetrahydroindolone derivative or analogue where A is a 9-atom bicyclic moiety in which the 5-membered ring has one to three nitrogen atoms, the bicyclic moiety having the structure of formula (XIV)



(XIV)

where:

(1) N_1 is bonded to L;

(2) A_2 and A_3 are C or N;

(a) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a single bond, then the bond between A_2 and R_2 is two single bonds, two hydrogen atoms or is a double bond in which R_2 is O or S and R_3 is two hydrogen atoms;

(b) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a double bond, then R_3 is hydrogen, the bond between A_2 and R_2 is a single bond and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(c) If A_2 and A_3 are both N, then the bond between A_2 and A_3 is a double bond and R_2 and R_3 are not present;

(d) If A_2 is N and A_3 is C, then the bond between A_2 and A_3 is a double bond, R_2 is not present, and R_3 is hydrogen;

(e) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a double bond, then R_3 is not present, the bond between A_2 and R_2 is a single bond, and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(f) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a single bond, then R_3 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkenyl, the bond between A_2 and R_2 is a double bond, and A_2 is O or S;

(3) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHQ_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl,

aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(4) $R_{5'}$ is hydrogen unless R_5 is alkyl, in which case R_5 is hydrogen or the same alkyl as R_5;

(5) R_5 and $R_{5'}$ can be taken together as a double bond to C_5, and can be O, S, NQ_3, or C which can be substituted with one or two groups R_5, where Q_3 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

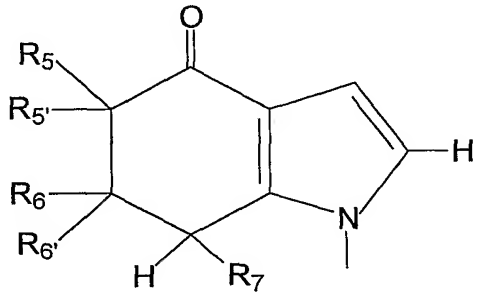
(6) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, NH_2, NHQ_4, NQ_4Q_5, OH, OQ_4, or SQ_4, where Q_4 and Q_5 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_4 and Q_5 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(7) $R_{6'}$ is hydrogen unless R_6 is alkyl, in which case $R_{6'}$ is hydrogen or the same alkyl as R_6;

(8) R_6 and $R_{6'}$ can be taken together as a double bond to C_6 and can be O, S, NQ_6, or C which can be substituted with one or two groups R_5, and where Q_6 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(9) R_7 is hydrogen unless R_5 is alkyl and $R_{5'}$ is hydrogen, in which case R_7 is the same alkyl as R_5.

Typically, A is a tetrahydroindolone moiety. More typically, the tetrahydroindolone moiety is a tetrahydroindolone moiety of formula (XV)



(XV)

in which:

(1) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NH_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

(2) $R_{5'}$ is hydrogen;

(3) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHW_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S and where W_1 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

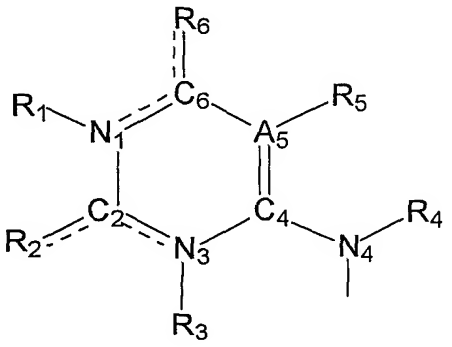
(4) $R_{6'}$ is hydrogen; and

(5) R_7 is hydrogen.

Typically, R_5, $R_{5'}$, R_6, $R_{6'}$, and R_7 are all hydrogen.

When A is a tetrahydroindolone moiety, preferred compounds are 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid ethyl ester and 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid.

In another alternative, the compound is a pyrimidine derivative or pyrimidine analogue. In this alternative, A is is an amino-substituted 6-membered heterocyclic moiety of formula (XVI)



(XVI)

where:

(1) if the bond between N_1 and the bond between C_6 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(2) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can

be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(3) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(4) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 and R_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3, where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(5) R_4 is hydrogen, alkyl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl;

(6) A_5 is carbon or nitrogen;

(7) if A_5 is nitrogen, then R_5 is not present;

(8) if A_5 is carbon, then R_5 is hydrogen, amino, alkyl, alkoxy, halo, nitro, aryl, cyano, alkenyl, or alkaryl;

(9) if R_5 and R_6 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl,

heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(10) N_4 is bonded to L.

Typically, A_5 is carbon and the 6-membered heterocyclic moiety is a pyrimidine moiety.

When A is a pyrimidine moiety, in one alternative, R_2 is O and R_3 is hydrogen. In this alternative, the pyrimidine moiety can be cytosine, thymine, uracil, 3-methyluracil, 3-methylthymine, 4-methylcytosine, 5-methylcytosine, 5-hydroxymethylcytosine, 5-hydroxyuracil, 5-carboxymethyluracil, or 5-hydroxymethyluracil.

In another alternative, R_2 is S and R_3 is hydrogen. In this alternative, the pyrimidine moiety can be 2-thiouracil, 5-methylamino-2-thiouracil, 5-methyl-2-thiouracil, or 2-thiocytosine.

In still another alternative, R_2 is amino and the bond between C_2 and N_3 is a double bond. In this alternative, the pyrimidine moiety can be 2-aminopyrimidinone or 2-amino-4-chloropyrimidine.

In still another alternative, R_2 is hydrogen and the bond between C_2 and N_3 is a double bond. In this alternative, the pyrimidine moiety can be 4-chloropyrimidine, 5-amino-4-chloropyrimidine, 4-chloro-5-methylpyrimidine, 4-chloro-5-hydroxymethylpyrimidine, or 4-chloro-5-carboxymethylpyrimidine.

In still another alternative, R_1 is hydrogen, methyl, or ethyl, R_5 is hydrogen, methyl, or ethyl, and R_6 is O. In this alternative, the pyrimidine moiety can be pyrimidinone.

Particularly preferred pyrimidine compounds include: 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester; 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid; 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino]

benzoic acid; and 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

In accordance with the present invention, and as used herein, the following terms, when appearing alone or as part of a moiety including other atoms or groups, are defined with the following meanings, unless explicitly stated otherwise. In addition, all groups described herein can be optionally substituted unless such substitution is excluded. The term "alkyl," as used herein at all occurrences, refers to saturated aliphatic groups including straight-chain, branched-chain, and cyclic groups, all of which can be optionally substituted. Preferred alkyl groups contain 1 to 10 carbon atoms. Suitable alkyl groups include methyl, ethyl, and the like, and can be optionally substituted. The term "alkenyl," as used herein at all occurrences, refers to unsaturated groups which contain at least one carbon-carbon double bond and includes straight-chain, branched-chain, and cyclic groups, all of which can be optionally substituted. Preferable alkenyl groups have 2 to 10 carbon atoms. The term "alkoxy" refers to the ether –O—alkyl, where alkyl is defined as as above. The term "aryl" refers to aromatic groups which have at least one ring having a conjugated π-electron system and includes carbocyclic aryl and biaryl, both of which may be optionally substituted. Preferred aryl groups have 6 to 10 carbon atoms. The term "aralkyl" refers to an alkyl group substituted with an aryl group. Suitable aralkyl groups include benzyl and the like; these groups can be optionally substituted. The term "aralkenyl" refers to an alkenyl group substituted with an aryl group. The term "heteroaryl" refers to carbon-containing 5-14 membered cyclic unsaturated radicals containing one, two, three, or four O, N, or S heteroatoms and having 6, 10, or 14 π-electrons delocalized in one or more rings, e.g., pyridine, oxazole, indole, thiazole, isoxazole, pyrazole, pyrrole, each of which can be optionally substituted as discussed above. The term "sulfonyl" refers to the group -S(O_2)-. The term "alkanoyl" refers to the group -C(O)Rg, where Rg is alkyl. The term "aroyl" refers to the group -C(O)Rg, where Rg is aryl. Similar compound radicals involving a carbonyl group and other groups are defined by analogy. The term "aminocarbonyl" refers to the group –NHC(O)-. The term "oxycarbonyl" refers to the group –OC(O)-. The term "heteroaralkyl" refers to an alkyl group substituted with a heteroaryl group. Similarly, the term "heteroaralkenyl" refers to an alkenyl group substituted with a heteroaryl group. As used herein, the term "lower," in reference to an alkyl or the alkyl portion of an another group including alkyl, is defined as a group containing one to six carbon atoms. The term "optionally substituted" refers to one or more substituents that can

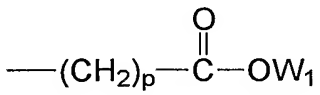
be lower alkyl, aryl, amino, hydroxy, lower alkoxy, aryloxy, lower alkylamino, arylamino, lower alkylthio, arylthio, or oxo, in some cases, other groups can be included, such as cyano, acetoxy, or halo. The term "halo" refers generally to fluoro, chloro, bromo, or iodo; more typically, "halo" refers to chloro.

As indicated above, the linker L is a hydrocarbyl moiety of 1 to 6 carbon atoms that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo. Preferably, the linker L has the structure $-(CH_2)_n-$ wherein n is an integer from 1 to 6. As detailed below, for most preferred embodiments of compounds useful in methods according to the present invention, a preferred linker has n equal to 2 or 3.

The moiety B is either: (i) –OZ, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; or (ii) $N(Y_1)$-D, where D is a moiety that promotes absorption of the compound, and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, which, when taken with D, can form a cyclic 5- or 6-membered saturated ring which can contain one other heteroatom which can be O, N, or S, of which N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S. Typically, Y_1 is hydrogen. Where the moiety B is –OZ, the moiety B is a carboxylic acid or carboxylic acid or ester. Typically, where B is a carboxylic acid ester, the moiety Z is a lower alkyl, such as methyl, ethyl, butyl, propyl, or isopropyl.

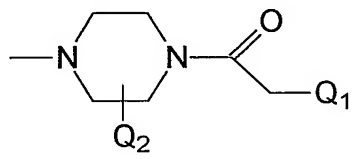
In one alternative, the moiety D, as described above, is a moiety having at least one polar, charged, or hydrogen-bond-forming group to improve the metabolic and bioavailability properties of the compound. The moiety D can be, but is not limited to, a moiety with physiological or biological activity such as nootropic activity. In one alternative, the moiety D can be a moiety containing at least one carboxyl, carboxamide, carboxyl ester, or carbonyl function. In another alternative, the moiety D can be a moiety containing at least one hydroxyl, primary amino, secondary amino, tertiary amino, sulfhydryl, or sulfonamidyl function. The moiety D can be cyclic or acyclic. Preferred examples of the moiety D are described below.

When the moiety D is a cyclic or acyclic moiety containing at least one carbonyl, carboxamide, carboxyl ester, or carbonyl function, in one preferred example, D is a carboxylic acid or carboxylic acid ester with the structure



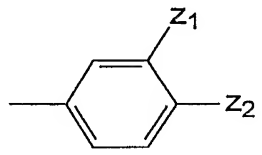
wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of hydrogen and lower alkyl. Typically, if W_1 is lower alkyl, it is methyl, ethyl, propyl, butyl, or isobutyl. Typically, p is 3. Typically, W_1 is hydrogen or ethyl.

In another preferred example, D and Y_1 are taken together to form a piperazine derivative as described in D. Manetti et al., "Molecular Simplification of 1,4-Diazabicyclo[4.3.0]nonan-9-ones Gives Piperazine Derivatives That Maintain High Nootropic Activity," J. Med. Chem. 43: 4499-4507 ("Manetti et al. (2000)"). B is an analogue of structure



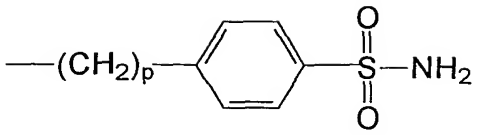
wherein Q_1 is hydrogen, methyl, ethyl, butyl, or propyl, Q_2 is hydrogen or methyl, where, if Q_2 is methyl, it can be located at either of the two possible positions in the piperazine ring.

In another preferred example, D has the structure



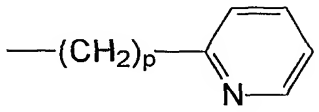
where one of Z_1 and Z_2 is hydrogen, and the other of Z_1 and Z_2 is –COOH or -$COOW_1$, wherein W_1 is alkyl. Typically, W_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, and isobutyl. Either of Z_1 or Z_2 can be hydrogen. When Z_1 is hydrogen and Z_2 is –COOH, the moiety B is *p*-aminobenzoic acid (PABA). When Z_1 is –COOH and Z_2 is hydrogen, the moiety B is *m*-aminobenzoic acid (MABA). When Z_1 is hydrogen and Z_2 is –$COOW_1$, the moiety B is an ester of *p*-aminobenzoic acid (PABA). When Z_1 is –$COOW_1$ and Z_2 is hydrogen, the moiety B is an ester of *m*-aminobenzoic acid (MABA). Typically, these esters are ethyl esters.

When the moiety D is a moiety that contains at least one hydroxyl, primary amino, secondary amino, tertiary amino, sulfhydryl, or sufonamidyl function, in one preferred example, D is a phenylsulfonamidyl moiety of structure



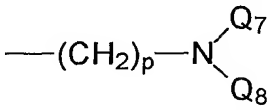
wherein p is an integer from 0 to 6. Typically, p is 2.

In another preferred example, D is an alkylpyridyl moiety of structure



wherein p is an integer from 1 to 6. Typically, p is 1.

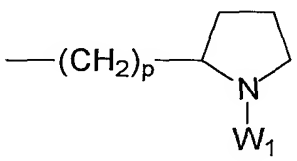
In another preferred example, D is a dialkylaminoalkyl moiety of the structure



wherein p is an integer from 1 to 6 and Q_7 and Q_8 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5 or 6 member ring which may contain 1 other heteroatom which can be N, O, or S, of which the N may be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

Where Q_7 and Q_8 can be taken together to form a five or six member ring, the ring is typically pyrrolidine, piperidine, or morpholine. The pyrrolidine ring can be optionally substituted with oxo. The piperidine ring can be optionally substituted with methyl or ethyl. Typically, p is 2 or 3.

In another preferred example, D is an alkylpyrrolidine moiety of the structure



wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of methyl, ethyl, and propyl. Typically, W_1 is methyl. Typically, p is 2.

Preferably, a compound useful in methods according to the present invention has a log P of from about 1 to about 4 in order to optimize bioavailability and CNS penetration of the compound.

Exemplary studies and treatments were performed as discussed below using various dosages and routes of administration of selected exemplary purine derivatives representative of compositions that are effective with the methods of the present invention. Of course, those skilled in the art will recognize that the present invention is not specifically limited to the particular compositions, dosages or routes of administration detailed below.

Depending upon the particular needs of the individual subject involved, the compositions used in the present invention may be administered in various doses to provide effective treatment concentrations based upon the teachings of the present invention. What constitutes an effective amount of the selected composition will vary based upon such factors including the activity of the selected compound, the physiological characteristics of the subject, the extent and nature of the subject's disease or condition and the method of administration. Exemplary treatment concentrations which have proven effective in modifying neural activity range from less than 1 μM to concentrations of 500 mM or more. Generally, initial doses will be modified to determine the optimum dosage for treatment of the particular mammalian subject. The compositions may be administered using a number of different routes including orally, topically, transdermally, intraperitoneal injection or intravenous injection directly into the bloodstream. Of course, effective amounts of the compounds may also be administered through injection into the cerebrospinal fluid or infusion directly into the brain, if desired.

The methods of the present invention may be effected using compounds administered to a mammalian subject either alone or in combination as a pharmaceutical formulation. Further, the compounds may be combined with pharmaceutically acceptable excipients and carrier materials such as inert solid diluents, aqueous solutions or non-toxic organic solvents. If desired, these pharmaceutical formulations may also contain preservatives and stabilizing agents and the like, as well as minor amounts of auxiliary substances such as wetting or emulsifying agents, as well as pH buffering agents and the like which enhance the effectiveness of the active ingredient. The pharmaceutically acceptable carrier can be

chosen from those generally known in the art, including, but not limited to, human serum albumin, ion exchangers, dextrose, alumina, lecithin, buffer substances such as phosphate, glycine, sorbic acid, potassium sorbate, propylene glycol, polyethylene glycol, and salts or electrolytes such as protamine sulfate, sodium chloride, or potassium chloride. Other carriers can be used.

Liquid compositions can also contain liquid phases either in addition to or to the exclusion of water. Examples of such additional liquid phases are glycerin, vegetable oils such as cottonseed oil, organic esters such as ethyl oleate, and water-oil emulsions.

The compositions can be made into aerosol formations (i.e., they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichloromethane, propane, or nitrogen. Other suitable propellants are known in the art.

Formulations suitable for parenteral administration, such as, for example, by intravenous, intramuscular, intradermal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions. These can contain antioxidants, buffers, preservatives, bacteriostatic agents, and solutes that render the formulation isotonic with the blood of the particular recipient. Alternatively, these formulations can be aqueous or non-aqueous sterile suspensions that can include suspending agents, thickening agents, solubilizers, stabilizers, and preservatives. Compositions suitable for use in methods according to the present invention can be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically, or intrathecally. Formulations of compounds suitable for use in methods according to the present invention can be presented in unit-dose or multi-dose sealed containers, in physical forms such as ampules or vials.

The invention is illustrated by the following Examples. These Examples are presented for illustration only and are not intended to limit the invention.

Example 1

Effect of Administration of the Bifunctional Purine Derivative N-4-Carboxyphenyl-3-(6-Oxohydropurin-9-yl) Propanamide on the Levels of Synaptophysin and sAPP Formation

Alzheimer's disease (AD) is characterized by a severe loss of presynaptic cholinergic neurons and decreased levels of acetylcholine and choline acetyltransferase in the cortex (1). Inhibition of cholinergic activity in the central nervous system (CNS) of patients with AD correlated with deterioration in scores on

dementia rating scales. Currently, cholinesterase inhibition is the most widely studied and developed approach for treating symptoms of AD. Because anticholinesterase drugs such as tacrine, donepezil, and rivastigmine only moderately improve symptoms in AD, an alternative cholinergic approach that is not entirely based on cholinesterase inhibition but that improves other known biochemical abnormalities associated with the disease should be tried.

One of the major neurochemical changes in AD is the cortical extracellular and vascular deposition of the amyloid beta-peptide (Aβ) which is derived from a large glycosylated membrane-bound beta-amyloid precursor protein (APP) (2). A constitutively expressed putative α-secretase enzyme bisects the Aβ domain within APP to release carboxyl-truncated soluble derivatives (sAPP) in conditioned media of cells (2). The goal of the work reported in this Example is to determine whether the drug AIT-082 can regulate the levels of Aβ.

AIT-082 is currently being investigated in clinical trials for the treatment of AD. It has been shown that AIT-082 can induce the expression of at least three neurotrophins: nerve growth factor (NGF), neurotrophin-3, and basic fibroblast growth factor (bFGF) (3). A combination of factors has been most effective in producing optimal trophic support for compromised neuron functions (3). However, the effects of AIT-082 and trophic factors on the regulation of sAPP and Aβ have not been clearly explored. It is reasonable to hypothesize that multiple trophic factors may synergistically regulate the processing of sAPP in a way that can lead to lower levels of Aβ. In the results reported in this Example, the level of sAPP in PC12 cells that were treated with NGF or AIT-082 was investigated.

Experimental Procedures

Materials. AIT-082 was obtained from NeoTherapeutics (Irvine, CA). Nerve growth factor (NGF) and basic fibroblast growth factor (bFGF) were procured from Life Technologies (Gaithersburg, MD). Other chemicals were of high purity and purchased from Sigma (St. Louis, MO).

Treatment of Cells and Preparation of Cell Extract. PC12 cells were first grown to 70-80% confluence in the regular medium. A day prior to the experiment, PC12 cells were subcultured uniformly onto the plate with minimum cellular aggregation/ clumping to approximately $1x10^6$ cells per 60-mm plate. The PC12 cells were then subjected to treatments with either AIT-082, NGF, bFGF or a combination as previously described (4). AIT-082 was added into separate plates at 11 different doses: 0, 5, 20, 30, 50, 100, 300 ng/ ml and also 1, 3, 10, 30, 100 μg/ ml. For

comparative purposes, cultures were treated with NGF at 10 and 50 ng/ ml, and bFGF was used at 50 ng/ml. Additional cultures contained both AIT-082 (300 ng/ml) and either NGF (50 ng/ml) or bFGF (50 ng/ml). Following incubation for 48 hours, the conditioned medium from each plate was collected.

PAGE and Western Immunoblotting. Total proteins from the conditioned media were analyzed on a 12% polyacrylamide gel containing SDS (SDS-PAGE), and western blot analysis was performed in the Mini-PROTEAN II system of Bio-Rad as described previously (6). sAPP was detected using the 22C11 (Boehringer Mannheim, Indianapolis, IN). A biotinylated secondary antibody, horse anti-mouse (Boehringer Mannheim), was also used. The detection system was based on the avidin-biotinylated-complex (Vector labs, Burlingame, CA) and enzymatic color reactions.

Results

Treatment of NGF or bFGF Results in a Substantial Increase in sAPP Secretion in PC12 Cells. In denaturing polyacrylamide gel, an equal amount of total protein was loaded from each of the conditioned medium samples. After 48 hours of incubation, 50 μg samples of conditioned media were subjected to SDS-PAGE (12%) and transferred to a nitrocellulose membrane. Protein size markers shown on the left of the blot from top to bottom are: 107, 74, 49.3, 36.4, and 28.5 kDa. For Figure 1, the transferred proteins were probed with anti-APP antibody (22C11), and immunodetection was carried out by the enzymatic color method as described previously (5). Two distinct bands of 110 and 95 kDa were detected, which correspond to soluble APP derivatives (sAPP) arising from different alternate forms of APP and/or their posttranslationally modified derivatives. The results suggest that with the NGF treatment (10 and 50 ng/ ml), a significant increase in the secretion of sAPP was observed (Fig. 1). NGF was previously shown to induce the release of sAPP from PC12 cultures (7). With the bFGF treatment, a slight increase in the secretion of sAPP was observed from the control. When the PC12 cells were incubated with different doses of AIT-082, a significant increase in sAPP was observed from the control (Fig. 1, lanes 5-8 vs. lane 1 and Figure 2). When the cells were simultaneously treated with AIT-082 and NGF, a significant increase in sAPP release was also observed (Fig. 1, lane 9 vs. lane 1), which was more than that in cells treated with either NGF or AIT-082 alone. A similar but smaller synergistic effect of bFGF and AIT-082 treatment was also observed (Figure 1, lane10 vs. lane1). Figure 2 demonstrates a dose response graph of the extracellular APP levels after culture of

cells with increasing levels of AIT-082. Concentrations of AIT-082 from 5-300 ng/mL yield statistically significantly higher levels of extracellular sAPP than control cultures.

References

The following references are referred to in Example 1:

1. R. Becker et al., "Alzheimer's Disease: Molecular Biology to Therapy" (Birkhauser, Boston, 1996).

2. D.J. Selkoe, "Alzheimer's Disease: Genotypes, Phenotype, and Treatment." Science 275: 630-631 (1997).

3. M.P. Rathbone et al., "AIT-082 as a Potential Neuroprotective and Regenerative Agent in Stroke and Central Nervous System Injury," Exp. Opin. Invest. Drugs 8: 1255-1262 (1999).

4. D.K. Lahiri et al., "Tacrine Alters the Processing of Beta-Amyloid Precursor Protein in Different Cell Lines," J. Neurosci. Res. 37: 777-787 (1994).

5. D.K. Lahiri & M.R. Farlow, "Differential Effect of Tacrine and Physostigmine on the Secretion of the Beta-Amyloid Precursor Protein in Cell Lines," J. Mol. Neurosci. 7: 41-49 (1996).

6. N.R. Marquez-Sterling et al., "Trafficking of Cell Surface-Amyloid Precursor Protein: Evidence that a Sorting Intermediate Participates in Synaptic Vesicle Recycling," J. Neurosci. 17: 140-151 (1997).

7. L.M. Repolo et al., "Nerve and Epidermal Growth Factors Induce the Release of the Alzheimer Amyloid Precursor from PC12 Cell Cultures," Biochem. Biophys. Res. Commun. 164: 664-670 (1989).

Example 2

Time Course of sAPP Secretion After Administration of AIT-082 to PC12 Cells

To determine the time course of sAPP secretion after administration of AIT-082 or NGF to PC12 cells, an experiment similar to the experiment of Example 1 was carried out using multiple time points. Five to six million PC12 cells were treated in RPMI 1640 and 0.5% FBS with doses of AIT-082 (10 nM-100 μM). NGF treatment resulted in sympathetic neuronal phenotypes in PC12 cells and cotreatment with AIT-082 enhanced NGF-mediated differentiation. Levels of sAPP in samples from conditioned media and cell lysates were measured by Western immunoblotting with anti-sAPP antibody. When PC12 cells were treated with AIT-082 for 6, 12, 24, 48, or 72 hours, there was an increase in levels of secreted sAPP. The increased sAPP secretion with AIT-082 treatment suggests that this compound may enhance the α-

secretase pathway and thereby could potentially decrease the amyloidogenic (amyloid formation) pathway.

Example 3

Effect of AIT-082 on the Amyloid Beta Peptide in PC12 cells

To determine the effect of AIT-082 on Aβ levels, PC12 cells were treated with a high dose of AIT-082 (100 μg/ ml) and the conditioned media was analyzed for Aβ. Levels of total Aβ were measured using a sensitive sandwich ELISA. Experiments were done in triplicate and the values were obtained from known standards run in parallel with the samples as described previously (A. Becher et al., "The Synaptophysin-Synaptobrevin Complex: A Hallmark of Synaptic Vessel Maturation," J. Neurosci. 19: 1922-1931). Our results suggest that there was a decrease in of secreted Aβ with AIT-082 treatment in PC12 cells as shown in Table 1.

Table 1. Effect of AIT-082 on the secretion of Aβ in cultured PC12 cells

Drug Treatment	Levels of total Aβ (fmols/ml)	Percent change from controls
Control	169 ± 3	-
AIT-082	136 ± 6	-20%

ADVANTAGES OF THE INVENTION

The present invention provides new methods for treating patients with a neurological disease or at risk for a neurological disease. The neurological disease to be treated or prevented can be a neurodegenerative disease, such as, but not limited to, Alzheimer's disease (AD). Alternatively, the neurological disease can be a neurodevelopmental disorder such as, but not limited to, Down's syndrome.

The present invention provides methods for increasing the secretion of sAPP and therefore decreasing the formation of Aβ. These methods can be combined with other treatments such as anticholinesterase treatments.

Although the present invention has been described in considerable detail, with reference to certain preferred versions thereof, other versions and embodiments are possible. Therefore, the scope of the invention is determined by the following claims.

We claim:

1. A method of either inhibiting the formation of Aβ or stimulating the formation of sAPP comprising administering to a patient with a neurological disease or a patient at risk of developing a neurological disease an effective amount of a compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP, the compound comprising: (1) a moiety A selected from the group consisting of a purine moiety, a purine analogue, a tetrahydroindolone moiety, a tetrahydroindolone analogue, a pyrimidine moiety, and a pyrimidine analogue; (2) a hydrocarbyl moiety L of 1 to 6 carbon atoms that is linked to the moiety A and that can be cyclic, with the hydrocarbyl moiety being optionally substituted with one or more substituents selected from the group consisting of lower alkyl, amino, hydroxy, lower alkoxy, lower alkylamino, lower alkylthio, and oxo; and (3) a moiety B that is linked to the moiety L through a carbonyl group wherein B is –OZ or $N(Y_1)$-D, where Z is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, aralkyl, or heteroaralkyl; D is a moiety that promotes absorption of the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP; and Y_1 is hydrogen, alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms, which can be N, O, or S.

2. The method of claim 1 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP passes through the blood-brain barrier.

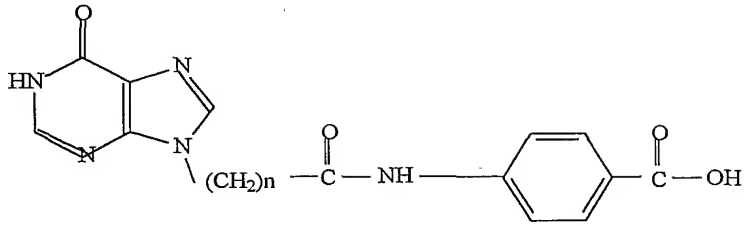
3. The method of claim 1 wherein A is a purine moiety.

4. The method of claim 3 wherein A is a substituted or unsubstituted hypoxanthine moiety.

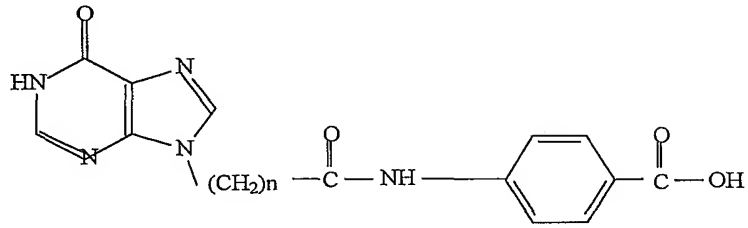
5. The method of claim 4 wherein L has the structure $–(CH_2)_n$-CONH- where n is an integer from 1 to 6.

6. The method of claim 5 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a

compound of formula (I)



where n is an integer from 1 to 6 and R is hydrogen or lower alkyl or is a salt or prodrug ester of a compound of formula (I)



wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl.

7. The method of claim 6 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a compound of formula (I) wherein n is an integer from 1 to 6 and R is hydrogen or lower alkyl.

8. The method of claim 7 wherein R is hydrogen.

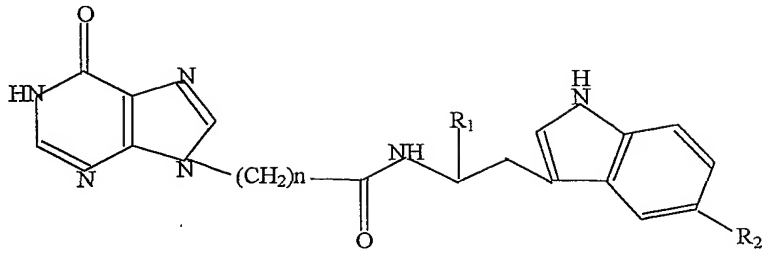
9. The method of claim 8 wherein n is 2 and the compound is N-4-[[3-(1,6-dihydro-6-oxopurin-9-yl)-1-oxopropyl] amino] benzoic acid.

10. The method of claim 7 wherein R is ethyl.

11. The method of claim 10 wherein n is 2 and the compound is N-4-[[3-(1,6-dihydro-6-oxopurin-9-yl)-1-oxopropyl] amino] benzoic acid ethyl ester.

12. The method of claim 5 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a

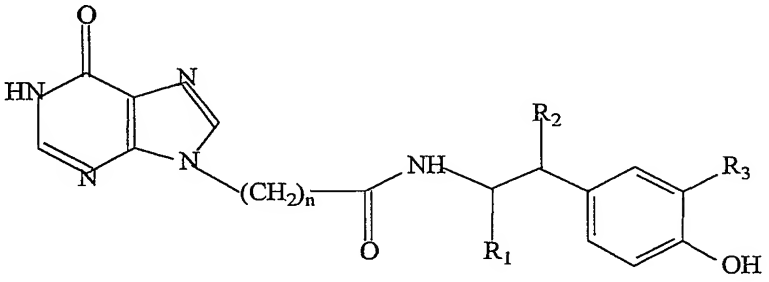
compound of formula (II)



wherein n is an integer from 1 to 6, R is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, and R_2 is selected from the group consisting of H and OH.

13. The method of claim 12 wherein n is 2.

14. The method of claim 5 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a compound of formula (III)



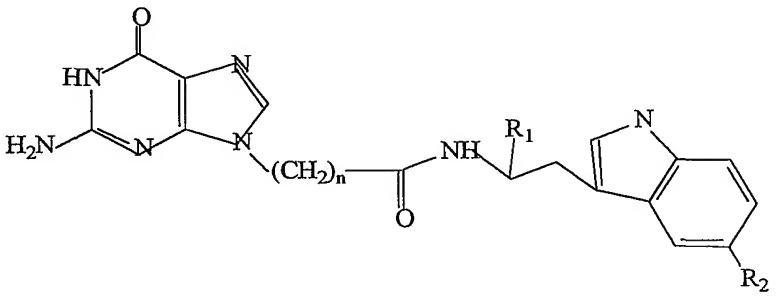
wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting from the group consisting of H and OH.

15. The method of claim 14 wherein n is 2.

16. The method of claim 3 wherein A is a substituted or unsubstituted guanine moiety.

17. The method of claim 16 wherein L has the structure $-(CH_2)_n$-CONH- wherein n is an integer from 1 to 6.

18. The method of claim 17 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a compound of formula (IV)



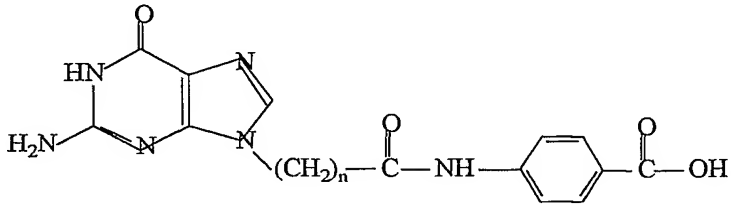
wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino and R_2 is selected from the group consisting of H and OH.

19. The method of claim 18 wherein n is 2, R_1 is H, and R_2 is OH, and the compound is N-(2-(5-hydroxyindol-3-yl)) ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

20. The method of claim 18 wherein n is 2, R_1 is H, and R_2 is H, and the compound is N-(2-(2-indol-3-yl)ethyl))-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

21. The method of claim 18 wherein n is 2, R_1 is COOH, and R_2 is OH, and the compound is N-(1-carboxyl-(2-(5-hydroxyindol-3-yl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

22. The method of claim 17 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a compound of formula (V)

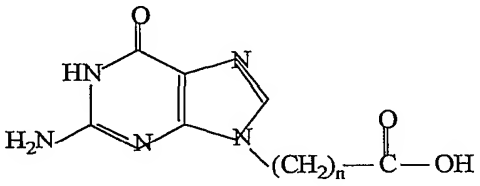


wherein n is an integer from 1 to 6 and R is selected from the group consisting of hydrogen and lower alkyl.

23. The method of claim 22 wherein n is 2, R is hydrogen, and the compound is N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

24. The method of claim 22 wherein n is 2, R is ethyl, and the compound is N-4-carboxyphenyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide ethyl ester.

25. The method of claim 17 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a compound of formula (VI)

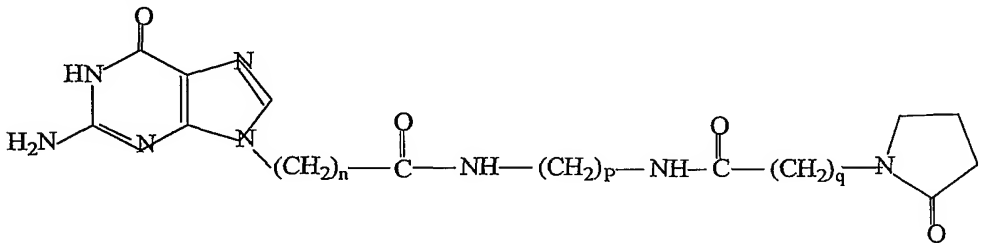


wherein n is an integer from 1 to 6 and R is selected from the group consisting of hydrogen and lower alkyl.

26. The method of claim 25 wherein n is 2, R is hydrogen, and the compound is 3-(2-amino-6-oxohydropurin-9-yl) propanoic acid.

27. The method of claim 25 wherein n is 2, R is ethyl, and the compound is 3-(2-amino-6-oxohydropurin-9-yl) propanoic acid ethyl ester.

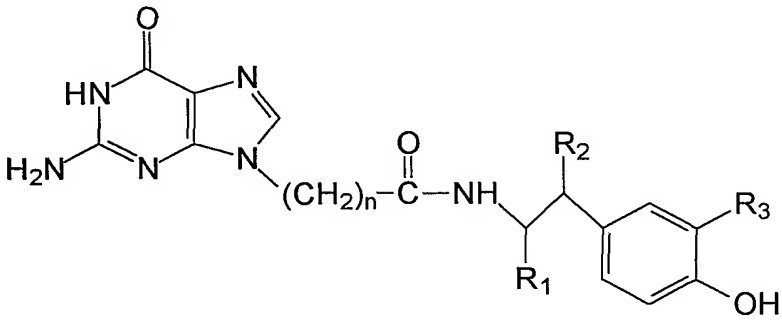
28. The method of claim 17 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a compound of formula (VII)



wherein n is an integer from 1 to 6, p is an integer from 1 to 6, and q is an integer from 1 to 3.

29. The method of claim 28 wherein n is 2, p is 2, and q is 1, and the compound is N-[2-[[2-(2-oxopyrrolidin-1-yl)-1-oxoethyl] amino] ethyl] propanamide.

30. The method of claim 17 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a compound of formula (VIII)



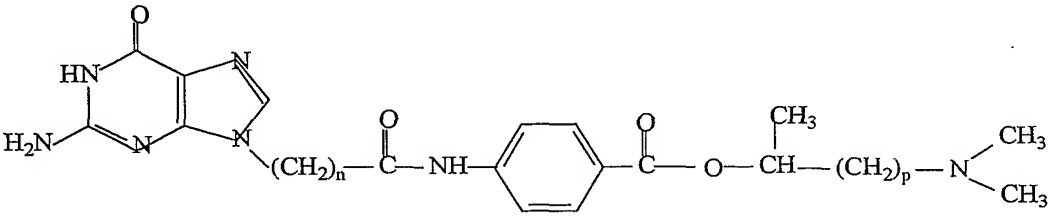
wherein n is an integer from 1 to 6, R_1 is selected from the group consisting of H, COOH, and $COOW_1$, wherein W_1 is selected from the group consisting of lower alkyl, amino, and lower alkylamino, R_2 is selected from the group consisting of H and OH, and R_3 is selected from the group consisting of H and OH.

31. The method of claim 30 wherein n is 2, R_1 is H, R_2 is H, and R_3 is OH, and the compound is N-(2-(3,4-dihydroxyphenyl)ethyl-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

32. The method of claim 30 wherein n is 2, R_1 is H, R_2 is OH, and R_3 is OH, and the compound is N-(2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

33. The method of claim 30 wherein n is 2, R_1 is COOH, R_2 is H, and R_3 is H, and the compound is N-(1-carboxyl-2-(3,4-dihydroxyphenyl)ethyl)-3-(2-amino-6-oxohydropurin-9-yl) propanamide.

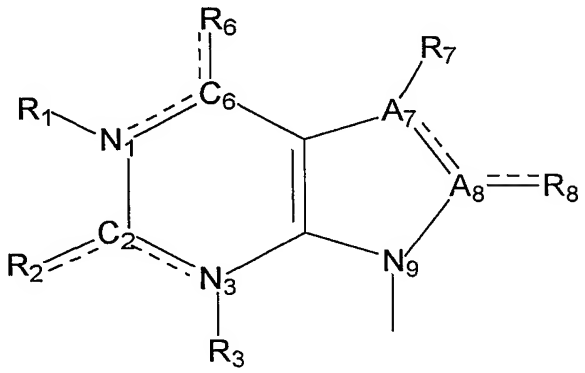
34. The method of claim 16 wherein the compound having the activity of either inhibiting the formation of Aβ or stimulating the formation of sAPP is a compound of formula (IX)



wherein n is an integer from 1 to 6 and p is an integer from 1 to 3.

35. The method of claim 34 wherein n is 2, p is 1, and the compound is N-4-[[3-(2-amino-6-oxohydropurin-9-yl) 1-oxopropyl] amino] benzoic acid 1-(dimethylamino)-2-propyl ester.

36. The method of claim 1 wherein A is a substituted or unsubstituted 9-atom bicyclic moiety in which the 5-membered ring has 1 to 3 nitrogen atoms, the bicyclic moiety having the structure of formula (X)



where:

(a) if the bond between N_1 and the bond between C_5 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(b) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(c) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(d) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(e) A_7 and A_8 are C or N;

(i) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a single bond, then the bond between A_8 and R_8 is two single bonds to two hydrogen atoms or is a double bond in which R_8 is O or S and R_7 is two hydrogen atoms;

(ii) if A_7 and A_8 are both C and the bond between A_7 and A_8 is a double bond, then R_7 is hydrogen, the bond between A_8 and R_8 is a single bond and R_8 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(iii) if A_7 and A_8 are both N, then the bond between A_7 and A_8 is a double bond, and R_7 and R_8 are not present;

(iv) if A_7 is C and A_8 is N, then the bond between A_7 and A_8 is a double bond, R_7 is hydrogen, and R_8 is not present;

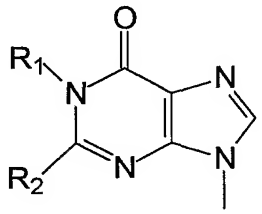
(v) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a double bond, then R_7 is not present, the bond between A_8 is a single bond, and R_8 is

hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(vi) if A_7 is N, A_8 is C, and the bond between A_7 and A_8 is a single bond, then R_7 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl, the bond between A_8 and R_8 is a double bond, and R_8 is O or S; and

(f) N_9 is bonded to L; with the proviso that A does not have the structure of an unsubstituted guanine or hypoxanthine.

37. The method of claim 3 wherein the purine moiety is a purine moiety of formula (XI)



in which:

(a) R_1 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, and heteroaralkyl; and R_2 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylokoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroarylkylaminocarbonyl in which the alkyl portions could be cyclic and can contain from one to three heteroatoms which could be N, O, or S, with the proviso that both R_1 and R_2 are not hydrogen and that R_1 is not hydrogen when R_2 is amino.

38. The method of claim 37 wherein R_1 is butyl and R_2 is hydrogen.

39. The method of claim 37 wherein R_1 is benzyl and R_2 is hydrogen.

40. The method of claim 37 wherein R_1 is dimethylaminoethyl and R_2 is hydrogen.

41. The method of claim 37 wherein R_1 is cyclopentyl and R_2 is hydrogen.

42. The method of claim 37 wherein R_1 is cyclohexylmethyl and R_2 is hydrogen.

43. The method of claim 37 wherein R_1 is cyclopropylmethyl and R_2 is hydrogen.

44. The method of claim 37 wherein R_1 is hydrogen and R_2 is phenyl.

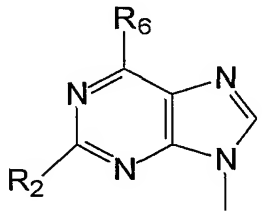
45. The method of claim 37 wherein R_1 is hydrogen and R_2 is butyl.

46. The method of claim 37 wherein R_1 is butyl and R_2 is butyl.

47. The method of claim 37 wherein R_1 is hydrogen and R_2 is methyl.

48. The method of claim 37 wherein R_1 is hydrogen and R_2 is phenylamino.

49. The method of claim 3 wherein the purine moiety is a purine moiety of Formula (XII)



in which:

(a) R_2 is selected from the group consisting of hydrogen, halo, amino, OQ_3, SQ_3, $NHNH_2$, $NHOQ_3$, NQ_3Q_4, or NHQ_3, where Q_3 and Q_4 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_3 and Q_4 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3 where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl,

aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(b) R_6 is selected from the group consisting of hydrogen, halo, amino, OQ_5, SQ_5, $NHNH_2$, $NHOQ_5$, NQ_5Q_6, or NHQ_6, where Q_5 and Q_6 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, and heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_5 and Q_6 are present together and are alkyl, they can be taken together to form a 5- or 6- membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylkoxycarbonyl, heteroarylkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

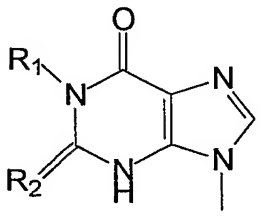
50. The method of claim 49 wherein R_2 is hydrogen and R_6 is amino.

51. The method of claim 49 wherein R_6 is chloro.

52. The method of claim 49 wherein R_6 is phenylamino.

53. The method of claim 49 wherein R_2 is amino and R_6 is chloro.

54. The method of claim 3 wherein the purine moiety is the purine moiety of Formula (XIII)



in which:

(a) R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl; and

(b) R_2 is O or S.

55. The method of claim 54 wherein R_1 is hydrogen.

56. The method of claim 54 wherein R_2 is O.

57. The method of claim 54 wherein R_2 is S.

58. The method of claim 3 wherein the compound is 4-[3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester.

59. The method of claim 3 wherein the compound is 4-[3-(1-butyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester.

60. The method of claim 3 wherein the compound is 4-[3-(1-methyl-6-oxo-1,6-dihydropurin-9-yl)propionylamino] benzoic acid ethyl ester.

61 The method of claim 3 wherein the compound is 4-[3-(1-2-dimethylaminoethyl)-6-oxo-1,6-dihydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

62. The method of claim 3 wherein the compound is 4-[3-(2,6-dioxo-1,2,3,6-tetrahydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

63. The method of claim 3 wherein the compound is 4-[3-(6-methoxypurin-9-yl) propionylamino] benzoic acid ethyl ester.

64. The method of claim 3 wherein the compound is 4-[3-(6-dimethylaminopurin-9-yl) propionylamino] benzoic acid ethyl ester.

65. The method of claim 3 wherein the compound is 4-[3-(2-amino-6-chloropurin-9-yl) propionylamino] benzoic acid ethyl ester.

66. The method of claim 3 wherein the compound is 4-[2-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

67. The method of claim 3 wherein the compound is 4-[2-(2-butyl-6-oxo-1,6-dihydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

68. The method of claim 3 wherein the compound is 4-[2-(6-oxo-2-phenyl-1,6-dihydropurin-9-yl) propionylamino] benzoic acid ethyl ester.

69. The method of claim 3 wherein the compound is 4-{[3-(6-chloropurin-9-yl) propionyl] methylamino} benzoic acid methyl ester.

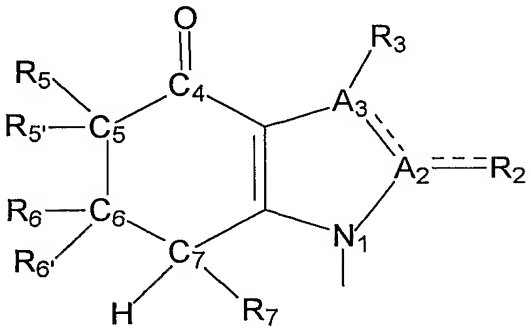
70. The method of claim 3 wherein the compound is 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-[3-(2-oxopyrrolidin-1-yl)propyl] propanamide.

71. The method of claim 3 wherein the compound is 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-{2-[2-(2-oxopyrrolidin-1-yl)acetylamino]ethyl} propanamide.

72. The method of claim 3 wherein the compound is N-[3-(2-oxopyrrolidin-1-yl)propyl]-3-(6-oxo-2-thioxo-1,2,3,6-tetrahydropurin-9-yl) propanamide.

73. The method of claim 3 wherein the compound is 3-(1-benzyl-6-oxo-1,6-dihydropurin-9-yl)-N-(3-morpholin-4-yl)propyl propionamide.

74. The method of claim 1 wherein the compound is a tetrahydroindolone derivative or analogue where A is a 9-atom bicyclic moiety in which the 5-membered ring has one to three nitrogen atoms, the bicyclic moiety having the structure of formula (XIV)



where:

(a) N_1 is bonded to L;

(b) A_2 and A_3 are C or N;

(i) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a single bond, then the bond between A_2 and R_2 is two single bonds, two hydrogen atoms or is a double bond in which R_2 is O or S and R_3 is two hydrogen atoms;

(ii) If A_2 and A_3 are both C and the bond between A_2 and A_3 is a double bond, then R_3 is hydrogen, the bond between A_2 and R_2 is a single bond and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(iii) If A_2 and A_3 are both N, then the bond between A_2 and A_3 is a double bond and R_2 and R_3 are not present;

(iv) If A_2 is N and A_3 is C, then the bond between A_2 and A_3 is a double bond, R_2 is not present, and R_3 is hydrogen;

(v) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a double bond, then R_3 is not present, the bond between A_2 and R_2 is a single bond, and R_2 is hydrogen, halo, alkyl, alkenyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, or heteroaralkenyl;

(vi) If A_2 is C, A_3 is N, and the bond between A_2 and A_3 is a single bond, then R_3 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, or heteroaralkenyl, the bond between A_2 and R_2 is a double bond, and A_2 is O or S;

(c) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHQ_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(d) $R_{5'}$ is hydrogen unless R_5 is alkyl, in which case R_5 is hydrogen or the same alkyl as R_5;

(e) R_5 and $R_{5'}$ can be taken together as a double bond to C_5, and can be O, S, NQ_3, or C which can be substituted with one or two groups R_5, where Q_3 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl,

heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(f) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, NH_2, NHQ_4, NQ_4Q_5, OH, OQ_4, or SQ_4, where Q_4 and Q_5 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_4 and Q_5 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom, which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

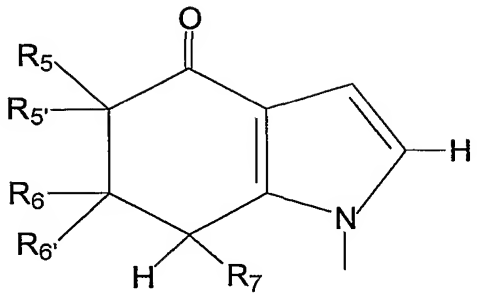
(g) $R_{6'}$ is hydrogen unless R_6 is alkyl, in which case $R_{6'}$ is hydrogen or the same alkyl as R_6;

(h) R_6 and $R_{6'}$ can be taken together as a double bond to C_6 and can be O, S, NQ_6, or C which can be substituted with one or two groups R_5, and where Q_6 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(i) R_7 is hydrogen unless R_5 is alkyl and $R_{5'}$ is hydrogen, in which case R_7 is the same alkyl as R_5.

75. The method of claim 74 wherein A is a tetrahydroindolone moiety.

76. The method of claim 75 wherein the tetrahydroindolone moiety is a tetrahydroindolone moiety of formula (XV)



in which:

(a) R_5 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NH_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

(b) $R_{5'}$ is hydrogen;

(c) R_6 is hydrogen, alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, NH_2, NHW_1, NQ_1Q_2, OH, OQ_1, or SQ_1, where Q_1 and Q_2 are aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S and where W_1 is alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from one to three heteroatoms which can be N, O, or S;

(d) $R_{6'}$ is hydrogen; and

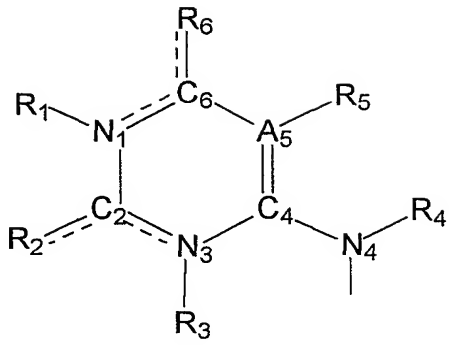
(e) R_7 is hydrogen.

77. The method of claim 76 wherein R_5, $R_{5'}$, R_6, $R_{6'}$, and R_7 are all hydrogen.

78. The method of claim 77 wherein the compound is 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid ethyl ester.

79. The method of claim 77 wherein the compound is 4-[3-(4-oxo-4,5,6,7-tetrahydroindolon-1-yl) propionylamino] benzoic acid.

80. The method of claim 1 wherein A is an amino-substituted 6-membered heterocyclic moiety of formula (XVI)



where:

(a) if the bond between N_1 and the bond between C_6 is a single bond, then the bond between C_6 and R_6 is a double bond, R_6 is O or S, and R_1 is hydrogen, alkyl, aralkyl, cycloalkyl, or heteroaralkyl;

(b) if the bond between N_1 and C_6 is a double bond, then the bond between C_6 and R_6 is a single bond, R_1 is not present, and R_6 is hydrogen, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(c) if the bond between C_2 and N_3 is a single bond, then the bond between C_2 and R_2 is a double bond, R_2 is O or S, and R_3 is hydrogen or alkyl;

(d) if the bond between C_2 and N_3 is a double bond, then the bond between C_2 and R_2 is a single bond, R_3 is not present, and R_2 is hydrogen, alkyl, aralkyl, cycloalkyl, heteroaralkyl, halo, amino, OH, OQ_1, SQ_1, $NHNH_2$, $NHOQ_1$, NQ_1Q_2, or NHQ_1, where Q_1 and Q_2 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, heteroaroyl, alkylsulfonyl, arylsulfonyl,

heteroarylsulfonyl, aralkylsulfonyl, or heteroaralkylsulfonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_1 and Q_2 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_3, where Y_3 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S;

(e) R_4 is hydrogen, alkyl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl;

(f) A_5 is carbon or nitrogen;

(g) if A_5 is nitrogen, then R_5 is not present;

(h) if A_5 is carbon, then R_5 is hydrogen, amino, alkyl, alkoxy, halo, nitro, aryl, cyano, alkenyl, or alkaryl;

(i) if R_5 and R_6 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S; and

(j) N_4 is bonded to L.

81. The method of claim 80 wherein A_5 is carbon and the 6-membered heterocyclic moiety is a pyrimidine moiety.

82. The method of claim 81 wherein R_2 is O and R_3 is hydrogen.

83. The method of claim 82 wherein the pyrimidine moiety is selected from the group consisting of cytosine, thymine, uracil, 3-methyluracil, 3-methylthymine, 4-methylcytosine, 5-methylcytosine, 5-hydroxymethylcytosine, 5-hydroxyuracil, 5-carboxymethyluracil, and 5-hydroxymethyluracil.

84. The method of claim 81 wherein R_2 is S and R_3 is hydrogen.

85. The method of claim 84 wherein the pyrimidine moiety is selected from the group consisting of 2-thiouracil, 5-methylamino-2-thiouracil, 5-methyl-2-thiouracil, and 2-thiocytosine.

86. The method of claim 81 wherein R_2 is amino and the bond between C_2 and N_3 is a double bond.

87. The method of claim 86 wherein the pyrimidine moiety is selected from the group consisting of 2-aminopyrimidinone and 2-amino-4-chloropyrimidine.

88. The method of claim 81 wherein R_2 is hydrogen and the bond between C_2 and N_3 is a double bond.

89. The method of claim 88 wherein the pyrimidine moiety is selected from the group consisting of 4-chloropyrimidine, 5-amino-4-chloropyrimidine, 4-chloro-5-methylpyrimidine, 4-chloro-5-hydroxymethylpyrimidine, and 4-chloro-5-carboxymethylpyrimidine.

90. The method of claim 81 wherein R_1 is hydrogen, methyl, or ethyl, R_5 is hydrogen, methyl, or ethyl, and R_6 is O.

91. The method of claim 90 wherein the pyrimidine moiety is pyrimidinone.

92. The method of claim 81 wherein the compound is 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

93. The method of claim 81 wherein the compound is 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

94. The method of claim 81 wherein the compound is 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

95. The method of claim 81 wherein the compound is 4-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

96. The method of claim 81 wherein the compound is 4-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

97. The method of claim 81 wherein the compound is 4-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

98. The method of claim 81 wherein the compound is 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

99. The method of claim 81 wherein the compound is 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

100. The method of claim 81 wherein the compound is 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid ethyl ester.

101. The method of claim 81 wherein the compound is 3-[3-(2-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

102. The method of claim 81 wherein the compound is 3-[3-(6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

103. The method of claim 81 wherein the compound is 3-[3-(5-amino-6-chloropyrimidin-4-ylamino) propionylamino] benzoic acid.

104. The method of claim 1 wherein L has the structure $-(CH_2)_n-$ wherein n is an integer from 1 to 6.

105. The method of claim 104 wherein n is 2.

106. The method of claim 104 wherein n is 3.

107. The method of claim 1 wherein the moiety B is –OZ.

108. The method of claim 107 wherein Z is hydrogen.

109. The method of claim 107 wherein Z is alkyl.

110. The method of claim 109 wherein Z is selected from the group consisting of methyl, ethyl, butyl, propyl, and isopropyl.

111. The method of claim 1 wherein B is $-N(Y_1)-D$.

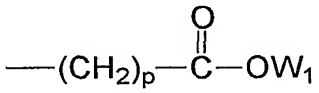
112. The method of claim 111 wherein Y_1 is hydrogen.

113. The method of claim 111 wherein Y_1 is lower alkyl.

114. The method of claim 113 wherein Y_1 is methyl.

115. The method of claim 111 wherein D is a moiety having at least one polar, charged, or hydrogen-bond-forming group to increase the water-solubility of the compound.

116. The method of claim 115 wherein D is a carboxylic acid or carboxylic acid ester with the structure

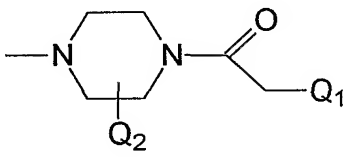


wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of hydrogen and lower alkyl.

117. The method of claim 116 wherein W_1 is hydrogen.

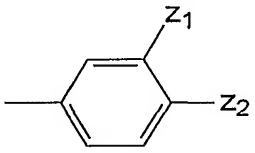
118. The method of claim 116 wherein W_1 is ethyl.

119. The method of claim 115 wherein D and Y_1 are taken together to form a piperazine derivative of the structure



wherein Q_1 is hydrogen, methyl, ethyl, butyl, or propyl, and Q_2 is hydrogen or methyl, where, if Q_2 is methyl, it can be located on either of the two possible positions in the piperazine ring.

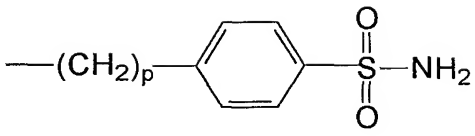
120. The method of claim 115 wherein D has the structure



wherein one of Z_1 and Z_2 is hydrogen and the other is Z_1 and Z_2 is –COOH or –$COOW_1$, wherein W_1 is alkyl.

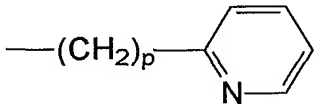
121. The method of claim 120 wherein W_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, and isobutyl.

122. The method of claim 115 wherein D is a phenylsulfonamidyl moiety of the structure



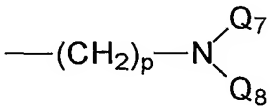
wherein p is an integer from 0 to 6.

123. The method of claim 115 wherein D is an alkylpyridyl moiety of the structure



wherein p is an integer from 1 to 6.

124. The method of claim 114 wherein D is an dialkylaminoalkyl moiety of the structure



wherein p is an integer from 1 to 6 and Q_7 and Q_8 are alkyl, aralkyl, heteroaralkyl, aryl, heteroaryl, alkanoyl, aroyl, aralkanoyl, heteroaralkanoyl, or heteroaroyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S, and when Q_7 and Q_8 are present together and are alkyl, they can be taken together to form a 5- or 6-membered ring which can contain one other heteroatom which can be N, O, or S, of which the N can be further substituted with Y_2, where Y_2 is alkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, aralkylaminocarbonyl, or heteroaralkylaminocarbonyl, in which the alkyl portions can be cyclic and can contain from 1 to 3 heteroatoms which can be N, O, or S.

125. The method of claim 124 wherein Q_7 and Q_8 are each alkyl.

126. The method of claim 125 wherein Q_7 and Q_8 are each selected from the group consisting of methyl, ethyl, propyl, butyl, and isobutyl.

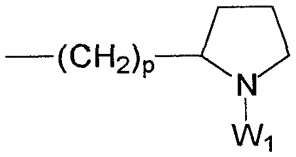
127. The method of claim 126 wherein Q_7 and Q_8 are taken together to form 5- or 6-membered optionally substituted ring.

128. The method of claim 127 wherein the ring is a morpholinyl ring.

129. The method of claim 127 wherein the ring is a pyrrolidinyl ring that is optionally substituted with oxo.

130. The method of claim 126 wherein the ring is a piperidinyl ring that is optionally substituted with methyl or ethyl.

131. The method of claim 115 wherein D is an alkylpyrrolidinyl moiety of the structure



wherein p is an integer from 1 to 6 and W_1 is selected from the group consisting of methyl, ethyl, and propyl.

132. The method of claim 1 wherein the compound has a log P of from about 1 to about 4.

133. The method of claim 1 wherein the neurological disease is a neurodegenerative disease.

134. The method of claim 133 wherein the neurodegenerative disease is Alzheimer's disease.

135. The method of claim 1 wherein the neurological disease is a neurodevelopmental disorder.

136. The method of claim 135 wherein the neurodevelopmental disorder is Down's syndrome.

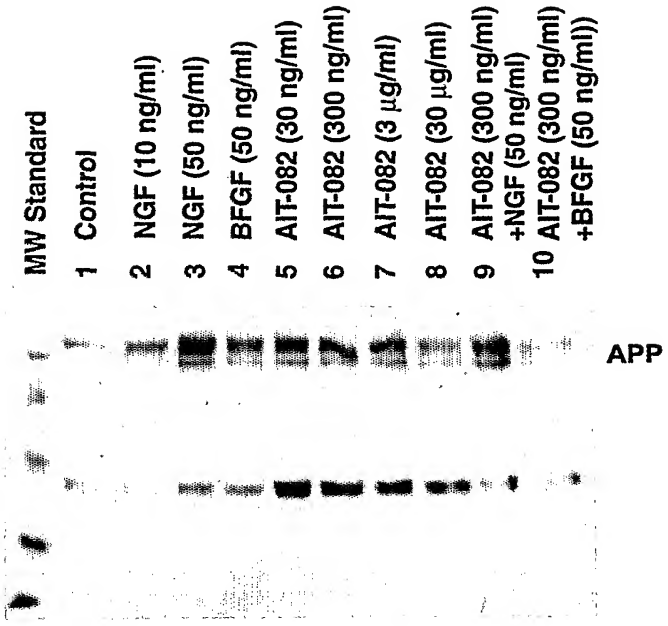
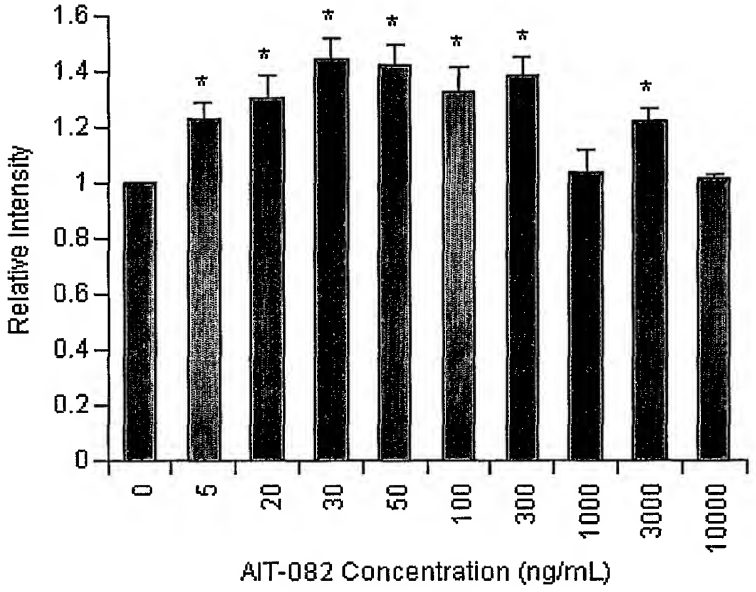

MW Standard
1 Control
2 NGF (10 ng/ml)
3 NGF (50 ng/ml)
4 BFGF (50 ng/ml)
5 AIT-082 (30 ng/ml)
6 AIT-082 (300 ng/ml)
7 AIT-082 (3 μg/ml)
8 AIT-082 (30 μg/ml)
9 AIT-082 (300 ng/ml)
+NGF (50 ng/ml)
10 AIT-082 (300 ng/ml)
+BFGF (50 ng/ml))
APP

Fig. 1



* designates statistically significantly different from control (i.e. 0 ng/mL)

Fig. 2

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WO 02/004450 A3

(54) Title: METHODS FOR PREVENTION OF ACCUMULATION OF AMYLOID BETA PEPTIDE IN THE CENTRAL NERVOUS SYSTEM

(57) Abstract: A method of either inhibiting the formation of Aβ or stimulating the formation of sAPP comprises administering to a patient with a neurological disease or a patient at risk of developing a neurological disease an effective quantity of a purine derivative or analogue, a tetrahydroindolone derivative or analogue, or a pyrimidine derivative or analogue. If the compound is a purine derivative, the purine moiety can be guanine or hypoxanthine. The neurological disease can be a neurodegenerative disease such as Alzheimer's disease or a neurodevelopmental disorder such as Down's syndrome. Typically, the compound can pass through the blood-brain barrier. The purine moiety can be hypoxanthine or guanine. A particularly preferred purine derivative is N-4- carboxyphenyl-3-(6-oxohydropurin-9-yl) propanamide.

INTERNATIONAL SEARCH REPORT

International Application No
I..,.S 01/21384

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/52 A61K31/405 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BEILSTEIN Data, BIOSIS, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 14434 A (A.J. GLASKY) 3 October 1991 (1991-10-03) page 7, lines 30-35; page 42, lines 15-18; pages 44-59	1-15, 107-116, 120-131, 133,134
A	idem	36,37

X	D.K. LAHIRI ET AL: "Annals of the New York Academy of Sciences, Vol. 903, pages 387-393" April 2000 (2000-04) , NEW YORK ACADEMY OF SCIENCES , NEW YORK, US; XP001040392 page 390, lines 18-40	1-9,111, 112,115, 120,133, 134
A	idem	36,37

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 May 2002	22. 08. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

International Application No
P(S 01/21384

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	B.R. BAKER ET AL: J. PHARM. SCI., vol. 54, no. 11, 1965, pages 1609-1616, XP001076681 table I, compounds XV, XVIII; scheme I, compounds XVI, XXII-XXVII, XXIX	1,3,36, 49-51, 107,108, 111,112, 115-117, 120,121
A	B.R. BAKER ET AL: J. PHARM. SCI., vol. 54, no. 12, 1965, pages 1774-1781, XP001076680 table I, compounds VIII, XXVI, XXVII	1,3,36, 107,108, 111,112, 115,120
A	WO 96 20711 A (UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER) 11 July 1996 (1996-07-11) page 3, lines 1-23; page 4, lines 14-29; page 5, line 25; page 8, lines 24-32	1,3,16, 36,37, 48,107, 108
A	M.A. PEETERS ET AL: JOURNAL OF NEUROLOGICAL SCIENCES, vol. 133, 1995, pages 31-41, XP001040393 the whole document	133-136
P,X	WO 01 29039 A (NEOTHERAPEUTICS INC) 26 April 2001 (2001-04-26) whole document, in particular formulae I-VII, X, XIII-XIV, XVIII, XXVI-XXVII, XXX, XXXII, XXXV, XL	1-3, 16-35, 107,108, 111,112, 115-117, 120-131, 133,134
A	idem	36,37

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 01/21384

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-136 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-2, 104-136 (in part); 3-73

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-2, 104-136 (in part); 3-73

   Compounds of the formula A-L-B of claim 1, wherein A is selected from the group consisting of a purine moiety and a purine analogue, for use in the treatment of neurological diseases.

2. Claims: 1-2, 104-136 (in part); 74-79

   Compounds of the formula A-L-B of claim 1, wherein A is selected from the group consisting of a tetrahydroindolone moiety and a tetrahydroindolone analogue, for use in the treatment of neurological diseases.

3. Claims: 1-2, 104-136 (in part); 80-103

   Compounds of the formula A-L-B of claim 1, wherein A is selected from the group consisting of a pyrimidine moiety and a pyrimidine analogue, for use in the treatment of neurological diseases.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 and 36 relate to an extremely large number of possible compounds for use in the treatment of neurological diseases. In fact, the claims contain so many variables and options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be sufficiently clear and concise, namely those parts relating to compounds of formula A-L-B of claim 1, wherein

A is a substituted or unsubstituted purine moiety covered by formula X of claim 36 for A7 is N and A8 is C and having any of the structures of formulae XI, XII or XIII (see claims 37, 49 or 54, respectively), an unsubstituted hypoxanthine moiety (see claim 4) or an unsubstituted guanine moiety (see claim 16).

L is a -(C1-6 straight or branched chain alkylene)-C(O)- linking group (see claims 6, 12, 14, 18, 22, 25, 28, 30, 34, 58-73) attached to N9 of the purine, hypoxanthine or guanine moiety (see claim 36, page 42, (f)), and

B is -OZ wherein Z is hydrogen or alkyl (see claims 108-110), or -N(Y1)-D wherein Y1 is hydrogen or alkyl (see claims 112-114) and D is as defined in claims 116-131 or is any of the D groups present in the compounds of claims 6, 12, 14, 18, 22, 25, 28, 30, 34, 58-73.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
P . US 01/21384

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